This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

1. (Amended) A method of detecting a target polynucleotide which comprises the steps of:

(a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another with:

(i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide;

(ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the second portion of the target polynucleotide and a flap region located adjacent to the first region; and

(iii) a reagent that is capable of cleaving the flap region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide;

under conditions such that the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region of the probe oligonucleotide is capable of hybridizing to form a complex that can be cleaved by the reagent to provide a reporter capable of being detected;

(b) obtaining a data set (t, S(t)), wherein t is time and S(t) is signal as a function of time, by detecting the reporter ~~to provide a signal~~ at a plurality of times; and

(c) ~~determining whether the signal exhibits a specific behavior as a function of time~~ transforming (t, S(t)) to provide a transformed data set (t*, S*(t*)) wherein t* and S*(t*) have minima of zero and maxima of unity, and determining whether the transformed data set exhibits non-linear behavior;

wherein the target polynucleotide is detected if the transformed data set exhibits non-linear behavior.

2. (Original) The method of claim 1 wherein the invader oligonucleotide comprises a first region that is capable of specifically hybridizing to the first portion of the target polynucleotide, and a flap region located adjacent to the first region.

3. (Original) The method of claim 2 wherein the flap region of the invader oligonucleotide is capable of specifically hybridizing to the target polynucleotide.

4. (Original) The method of claim 2 wherein flap region of the invader oligonucleotide is not capable of specifically hybridizing to the target polynucleotide.

5. (Original) The method of claim 2 wherein flap region of the invader oligonucleotide comprises a first section that is not capable of specifically hybridizing to the target polynucleotide, and a second section that is capable of specifically hybridizing to the target polynucleotide.

6. (Canceled).

7. (Canceled).

8. (Original) The method of claim 1 wherein the second portion of the target polynucleotide is located immediately 3' to the first portion of the target polynucleotide.

9. (Original) The method of one of claims 2-5 wherein the flap region of the invader oligonucleotide is located immediately 3' to the first region of the invader oligonucleotide, and the flap region of the probe is located immediately 5' to the first region of the probe.

10. (Original) The method of claim 1 wherein the signal is fluorescence or phosphorescence.

11. (Original) The method of claim 1 wherein the determination of whether the signal exhibits a specific behavior as a function of time is performed in real time.

12. (Canceled).

13. (Canceled).

14. (New) The method of claim 1 wherein the non-linear behavior is quadratic.

15. (New) A method of detecting a target polynucleotide which comprises the steps of:

(a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another with:

(i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide;

(ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the second portion of the target polynucleotide and a flap region located adjacent to the first region; and

(iii) a reagent that is capable of cleaving the flap region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide;

under conditions such that the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region of the probe oligonucleotide is capable of hybridizing to form a complex that can be cleaved by the reagent to provide a reporter capable of being detected;

(b) obtaining a data set (t, S(t)), wherein t is time and S(t) is signal as a function of time, by detecting the reporter at a plurality of times; and

(c) fitting (t, S(t)) to a quadratic function, transforming the quadratic function to yield a transformed function having independent and dependent variables having minima of zero and maxima of unity, and determining whether the transformed function exhibits non-linear behavior;

wherein the target polynucleotide is detected if the transformed function exhibits non-linear behavior.

16. (New) The method of claim 15 wherein the non-linear behavior is quadratic.

## REMARKS

Claims 1-5, 8-11 and 14-16 are pending in this application. Claim 1 has been amended and claims 6, 7, 12 and 13 have been canceled without prejudice to Applicants' right to pursue the subject matter they recite in one or more continuation, divisional or continuation-in-part applications.

Amended claim 1 is directed to an embodiment of the invention wherein a data set is transformed to provide a transformed data set (t*, S*(t*)) wherein t* and S*(t*) have minima of zero and maxima of unity, and wherein the target polynucleotide is detected by determining whether the transformed data set exhibits non-linear behavior. New independent claim 15 is directed to an embodiment of the invention wherein a data set is fit to a quadratic function, which is then transformed to yield a transformed function having independent and dependent variables having minima of zero and maxima of unity, and wherein the target polynucleotide is detected by determining whether the transformed function exhibits non-linear behavior. Support for the new and amended claims can be found on pages 9-13 of the application as filed. No new matter has been added.

### A. The Priority Date of this Application is March 27, 2000

Applicants first wish to thank the Examiner for the courtesy he extended their attorney, Max Bachrach, during a telephone conversation held June 3, 2003 concerning the priority date of this application.

As discussed, this application was filed on March 26, 2001, less than one year after the March 27, 2000 filing of provisional application no. 60/192,606, to which this application claims priority. On January 11, 2002, Applicants received a Notice of Omitted Item(s), which concerned a figure filed with the provisional application but inadvertently omitted from the papers constituting this application. Applicants subsequently filed a Preliminary Amendment, deleting all references to that figure.[1] Consequently, this application is entitled to the originally claimed March 27, 2000 filing date.

### B. The Rejections Under 35 U.S.C. § 112 Should be Withdrawn

On page 2 of the Office Action, claims 1-13 are rejected as allegedly indefinite, under 35 U.S.C. § 112, second paragraph. In particular, it is alleged that the step of "determining

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[1] Applicants respectfully draw the Examiner's attention to the Preliminary Amendment, filed January 16, 2003, and the Request for Correction of Official Filing Receipt, filed June 3, 2003 in connection with this case.

whether the signal exhibits a specific behavior as a function of time," which is recited by claim 1, is not correlated with the step of detection, recited by the preamble of that claim. Claim 1 has been amended to expressly recite this correlation. The rejection under § 112 should be withdrawn.

### C. The Rejections Under 35 U.S.C. § 102 Should be Withdrawn

On pages 3-9 of the Office Action, claims 1-3 and 8-10 are rejected as allegedly anticipated by Ryan *et al.*, *Molecular Diagnostics*, 4(2):135-144 (1999) ("Ryan") and Lyamichev *et al.*, *Nature Biotechnology*, 17:292-296 (1999) ("Lyamichev"). Claims 1-5 and 8-10 are also rejected as allegedly anticipated by U.S. patent no. 5,994,069 to Hall *et al.* ("Hall"). These rejections should be withdrawn for the following reasons.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in ... [the] claim." *Manual of Patent Examining Procedure* (MPEP) § 2131 (8th ed., August 2001); and *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

As the Examiner points out, each of the rejections under § 102 is based "upon a broad interpretation of the phrase 'specific behavior as a function of time.'" Office Action, pages 4, 5 and 8. Like amended claim 1, new independent claim 15 recites non-linear behavior. None of the cited references disclose the determination of whether a time-dependent signal or a function fit to a time-dependent signal is non-linear. For this reason alone, the rejections should be withdrawn. In addition, none of the cited references disclose the transformation of a data set or a function fit to a data set, as recited by claims 1 and 15, respectively. Therefore, Applicants respectfully request that the rejections under § 102 be withdrawn.

### D. The Rejections Under 35 U.S.C. § 103 Should be Withdrawn

On pages 9-13 of the Office Action, claim 1-13 are rejected as allegedly obvious over Hall in view of U.S. patent no. 6,387,621 to Wittwer ("Wittwer"). This rejection should be withdrawn for the following reasons.

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995); *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, the Patent

Office must first show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, it must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant' s disclosure. Third, the Patent Office must show that the prior art teaches or suggests all the claim limitations. MPEP § 2143; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). These criteria must be satisfied with factual and objective evidence found in the prior art: an examiner's conclusory statements cannot form a basis for a *prima facie* case of obviousness. *In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002).

As discussed above, Hall does not disclose or suggest the determination of whether a time-dependent signal or a function fit to a time-dependent signal is non-linear, nor does it disclose or suggest the transformation of a data set or a function fit to a data set, as recited by independent claims 1 and 15, respectively. Wittwer does not cure this deficiency.

Wittwer does not disclose an invasion assay. Instead, Wittwer discloses a method of compensating for baseline drift in PCR experiments. Wittwer, col. 2, lines 14-44. According to that method, PCR fluorescence background "is identified by selecting [a] sliding window ... with the shallowest slope." *Id.*, col. 6, lines 57-59. Admitting that this method of identifying a baseline does not always work, Wittwer then discusses the combined use of derivatives and "sliding window analysis" to determine which portions of a fluorescence curve exhibit the shallowest slope. *Id.*, col. 7, lines 5-37.

Independent claims 1 and 15 recite methods of detecting a target nucleotide which comprise the transformation of time-dependent data or a function fit to time-dependent data, respectively, to a specific transformation space. This transformation provides a facile, real-time means by which data obtained from an invasion assay can be distinguished from background noise. *See, e.g.*, Specification, page 11, line 30 - page 12, line 1. Moreover, it does not require the clumsy "sliding window analysis" required by Wittwer. Therefore, even if some motivation did exist, prior to this invention, to combine Hall and Wittwer—an assumption with which Applicants respectfully disagree—their combination does not disclose or suggest all of the limitations recited by the pending claims. Applicants respectfully request that the rejection under § 103 be withdrawn.

**E. Conclusion**

As discussed above, all of the pending claims are in condition for allowance.

No fee is believed due for this response. However, if a fee is due, please charge such fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Respectfully submitted,

Date August 14, 2003

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Enclosure